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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/049,373 | 06/21/2002 | Isao Ishida | 051023-0115 | 3667 |

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| EXAMINER | |
|---|---|
| TON, THAIAN N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/049,373 | ISHIDA ET AL. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-6 and 9-25* is/are pending in the application.

4a) Of the above claim(s) *6 and 10-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 9, 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/25/05 has been entered.

Applicants' Response and Amendment, filed 7/25/05, has been considered and entered. Claims 1, 3-6 and 9-25 are pending; claims 6 and 10-24 are withdrawn; claims 1, 3-5, 9 and 25 are under current examination.

The Ohshima Declaration, filed 7/25/05, has been considered but is not persuasive.

### *Election/Restrictions*

Claims 6 and 10-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/4/04.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8, 9 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The claimed invention consists of a mouse comprising at least one cell that comprises a human chromosome fragment that is not integrated into the mouse cell genome, wherein the human chromosome fragment expresses at least one human cytochrome P450 3A family gene. In specific embodiments, the human chromosome fragment is introduced by microcell fusion, the mouse is a chimeric mouse, and the expression of human cytochrome P450 3A gene is regulated by the control region of human cytochrome P450 3A family gene and is induced by a compound which induces the expression of a human cytochrome P450 3A family gene. The claims are also directed to cells, organs or tissues obtained from this mouse.

The specification teaches working examples, wherein the human chromosome 7 fragment, designated E22, is used to produce chimeric mice. See Examples, 1 and 4, for example. Particularly, the specification cites the method of WO 97/07671, to produce a mouse A9 cell library, harboring various human chromosomes. The '671 document is in Japanese, however, the Examiner notes that Tomizuka *et al.* (**Nature Genetics**, 16: 133-143 (1997), cited as Document A6 on Applicants' IDS, filed 6/21/02), teaches the general methodology of the production of chimeric mice expressing particular human chromosomes. In particular, they teach the microcell mediated-chromosome transfer method (MMCT) that is taught in the instant specification. See Figure 1. MMCT relies upon the spontaneous fragmentation of human chromosomes by irradiation, and the isolation of the resultant fragments

and identification of the fragments by PCR (see pp. 140-141, Methods & Materials). The instant specification teaches the generation of the E22 fragment by this MMCT method, and use of this particular fragment to produce chimeric mice.

As the E22 fragment is essential to the claimed method, it must be obtainable in a repeatable method set forth in the specification or otherwise be readily available to the public. If the E22 fragment is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make" may be satisfied by a deposit of the E22 fragment. The specification does not disclose a repeatable process to obtain the E22 fragment because it teaches the generation of the fragment by spontaneous fragmentation by irradiation, and it is not apparent if it is readily available to the public. If Applicants feel that the production of E22 fragment is disclosed by a repeatable process, Applicants are invited to point to specific support in the specification by page and line number.

If the deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the E22 fragment has been deposited under the Budapest Treaty and that the E22 fragment will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807);

and,

(e) the deposit will be replaced if it should ever become inviable.

Once the deposit has been perfected, the claims will be limited to the E22 fragment.

The breadth of the claims are not found to be enabling, because the specification teaches the production of one human chromosome fragment, E22, (see p. 58, lines 12-14), which is produced by MMCT, which spontaneously fragments chromosomes. The specification fails to provide any other guidance for any other chromosome fragments that express at least one human cytochrome P450 3A family gene, other than the E22 fragment.

Applicants' argue that the human chromosome #7 fragment that is introduced into the mouse cell predictability expresses all of the disclosed CYP3A family genes, but it is not essential to know how many cells in the claimed mouse need to be induced, for example, by rifampicin, in order for the mouse to be useful. Applicants point to the instantly-filed specification, to show that the presence of these three genes on the human #7 chromosome fragment using PCR and gene-specific primers. Applicants further argue that they do not need to provide any working examples to corroborate a well-established and predictable gene system. Applicants then point to the Ohshima Declaration for support. The Ohshima Declaration states that the chromosome fragment has various genes from the CYP3A family, and that the chimeric mice of the claimed invention express CYP3A5 and CYP3A7 genes (see p. 2, #6-10). They teach that they reproduced a fragment

similar to the one prepared in Example 23, and that it is slightly shorter than the one described in the specification. See #11. They teach that a chimeric mouse was produced according to the methods of the specification, and that the presence of CYP3A4, CYP3A5 and CYP3A7 genes were confirmed. See #12-13 of the Declaration.

The Applicants' arguments and Ohshima Declaration have been considered, but are not found to be fully persuasive. The instantly-filed specification does not provide guidance as to how to make and use the claimed mouse. The Examiner agrees that it is not essential to know how many cells of the claimed mouse would need to be induced, in order for the mouse to be useful. Particularly, the specification provides sufficient guidance with regard to how one would use a mouse having the cytochrome P450 gene, because of the art-recognized functions of P450, for example, in the metabolism of drugs. See Background section of specification. The claimed invention is not found to be enabled, because the fragment, which is used in the working examples is not found to be predictably produced. The Ohshima declaration states that they have "reproduced a human chromosome #7 fragment, similar to the one in Example 23". See #11 of the Declaration. Example 23 teaches the construction of a HAC having the chromosome #7 fragment, and a chromosome #14 fragment, SC20. The specification teaches that the homologous clones, obtained in Example 20 were used to produce this HAC (see p. 134, lines 23-27). Example 20 details the site-specific insertion of the loxPHyg cassette on the human chromosome fragment obtained in Example 19. Example 19 teaches the transfection of targeting vectors prepared in example 18 to DT40-#7 cells, obtained in Example 14, to insert a human telomere sequence to the genome region AF006752, thereby cleaving chromosome 7 in the inserted site. Example 14 teaches the introduction of the human chromosome 7 into chicken DT40 cells, using microcells purified from mouse A9 cells harboring the human chromosome 7. The mouse A9 cells, which were found to harbor human chromosome 7 fragments are

taught in the specification in Example 1, and the particular fragment is specifically identified as E22. Thus, it cannot be determined from the Declaration if Applicants are teaching the construction of a HAC, having both a chromosome 7 and 14 fragment, and further using the specification as guidance, it appears that the fragment that is used in the Declaration is the E22 fragment. Thus, if the Declaration is directed to utilizing the E22 fragment, this fails to provide any predictability with regard to the production of chromosome fragments, as broadly claimed, particularly, any chromosome fragment that expresses at least one human cytochrome P450 3A family gene (wherein the specification teaches only one fragment, E22, which is isolated from one particular chromosome, human chromosome #7).

The Declaration teaches that the fragment, which is similar to that of Example 23, is used to produce a chimeric mouse in accordance with Examples 24-26 of the specification. See #12. This is not persuasive. The specification indicates that the mice in Examples 24-26 also have an additional fragment from chromosome #14, SC20. Thus, the mice that are discussed in the specification are not analogous to that which is instantly claimed, as they have an additional chromosome fragment, and thus, methods of utilizing those mice are not analogous to what is instantly claimed. The Declaration states that CYP3A5, A7 and A4 genes are specifically expressed in the mouse liver and small intestine. See #14 and Figure 1 of Exhibit A. This is not persuasive because it is not clear if the expression analysis is directed to the mice that Applicants have made wherein the mice have both chromosome #14 and 7 fragments, or mice which only have a human chromosome a human cytochrome P450 3A gene family gene.

The Declaration further states that CYP3A5 and CYP3A7 is inducible with Rifampicin (#15) and that inducing P450 genes using Rifampicin is art-recognized to investigate the induction of cytochrome P-450 by xenobiotics (#19-21) and provide Kostrubsky *et al.* to provide evidence for this. The Declaration further teaches that

there is no question that researches in the field were confident, at the time the present invention was made, to appropriately induce gene expression and activity, and such induced CYP3A activity was sufficient to study the metabolic consequences of the subsequently-administered drug.

This is not persuasive. There is no guidance provided by the instantly-filed specification that the mice that are taught in the working examples, would express, upon administration of rifampicin, will express CYP3A5, A7 or A4. This is because, as stated above, the mice that are taught in the Declaration do not appear to be analogous to the instantly claimed mice. In particular, the Declaration teaches that mice that have 2 chromosome fragments would express these genes. However, the specification is silent with regard to the induction of the expression of these genes in mice that only have one chromosome 7 fragment. Thus, without sufficient guidance as to if these genes will express in the mice provided in the working examples and are instantly claimed, the mice fail to have an enabled use.

With particular regard to the claimed embodiment of an organ which is isolated from the claimed mice (see claim 9), these organs fail to have an enabled use. The specification provides no guidance as to how one of skill in the art would use the organs, as such, using these organs would require undue experimentation.

Accordingly, in view of the lack of teachings or guidance provided by the specification, or the Ohshima Declaration, with regard to the production of human chromosome fragments which express at least one human cytochrome P450 3A family gene, other than the exemplified fragment, E22, the lack of teachings or guidance provided by the Declaration, with particular regard to the particular mouse used, and lack of correlation between the mouse in the Declaration and the mouse as taught in the specification, the lack of an enabled use for the isolated organs, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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